Best of the AUA Annual Meeting

Highlights From the 2011 American Urological Association Meeting, May 14-19, 2011, Washington, DC

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Over 2300 posters, abstracts, and videos were presented at the 2011 annual meeting of the American Urological Association (AUA), held this year in Washington, DC, from May 14 through 19. The editors of *Reviews in Urology* have culled the enormous volume of information from this premier source and present here the findings most relevant to the practicing urologist.

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Prostate Markers

As has been the case for at least two decades, prostate markers were the subject of a large percentage of the abstracts presented at this year's annual meeting.

Vickers and colleagues[1] carried out an interesting study to assess how soon men at high risk for prostate cancer death can be identified. Capitalizing on a cardiovascular research study bank in Sweden, the researchers evaluated men aged 33 to 50 years with prostate-specific antigen (PSA) measured in archived plasma. A nested case-control design was employed, with three controls for each prostate cancer death. A single PSA reading at age 44 to 50 years was strongly predictive of prostate cancer death at a median follow-up of 27 years. Forty-four percent of deaths occurred in men at the 10th percentile of serum PSA level (1.5 ng/mL). This is an important study and is giving support to the notion of stratifying men for interval early detection testing based on initial PSA results.

The importance of nadir PSA during androgen deprivation therapy (ADT) was investigated by Keto and colleagues.[2] Men who were treated with ADT for biochemical recurrence from the SEARCH data base were studied (322 patients). PSA nadir, the lowest level obtained during follow-up, was analyzed. During a median follow-up of 51 months, the nadir level correlated with castration-resistant prostate cancer (CRPC), development of metastases, and prostate cancer–specific mortality. Relative to men with undetectable nadir, a PSA $>$ 0.2 ng/mL identified the greatest risk of progression.

Although we often do not recognize it as an important marker, testosterone (T) in the setting of ADT truly is. Numerous studies have demonstrated better outcomes in men with

lower and longer nadir T level compared with others on ADT. Pickles and Tyldesley[3] studied T levels exceeding castration thresholds of 20, 32, and 50 ng/dL; 2290 men on continuous luteinizing hormone-releasing hormone (LHRH) therapy were assessed. The risk of breakthrough T was 26.8%, 6.6%, and 3.3%, respectively, per patient course of ADT. Predisposing factors included younger age and higher body mass index (BMI), but not baseline T.

Crawford and associates[4] looked at baseline T levels in men on continuous ADT from two large clinical trials; 1669 men were evaluated. There were 1159 men from a trial of fracture prevention with toremifene citrate, 80 mg (any indication for ADT), and 510 men from a trial of sipuleucel-T (metastatic CRPC). Both trials required serum T $<$ 50 ng/mL at baseline; 18.3% had T $>$ 20 ng/dL. BMI correlated with men with higher T levels, although this did not persist in the subset of men who underwent orchiectomy. Neither patient age nor duration of ADT predicted men who had serum T $>$ 20 ng/dL. With the increasing evidence that the historically established definition of castration (T $<$ 50 ng/dL) may not be adequate in all men, these two presentations demonstrate that increasing use of serum T determination in men on ADT is warranted.

van der Sluis and colleagues[5] addressed the issue of what the true castrate level of T is in men following LHRH therapy or surgical castration. They correctly pointed out that the oft-cited level of 50 ng/dL is based on a less reliable assay; they used liquid chromatographic-tandem mass spectrometry in their study, which is considered a more accurate method for measuring T in the low range. Orchiectomy or LHRH agonist therapy was performed in 14 and 32 patients, respectively. At an interval of at least 3 months following ADT, all men had T $<$ 50 ng/dL. The median level was 3.9 ng/dL in men on LHRH agonist and 8.4 ng/dL in men surgically treated. All but one patient on LHRH therapy had T $<$ 20 ng/dL.

There were many presentations based on the prostate cancer antigen-3 (PCA3) gene. Shikanov and colleagues[6] evaluated its utility in monitoring men on active surveillance. Confirmatory repeat biopsy demonstrating Gleason score $>$ 6, more than 3 positive cores, or more then 50% involvement of a single core was considered unfavorable. The PCA3 urinary median level was 30 and 54 in those men with favorable and unfavorable pathology, respectively.

Goode and coworkers[7] compared the utility of PCA3 gene expression in initial and repeat biopsies in 289 men with an initial biopsy and 167 of those with a repeat biopsy. Although PCA3 was a better predictor of cancer on the initial biopsy, area under the curve (AUC) analysis demonstrated that there was no significant difference between PSA and PCA3's ability to predict cancer in men undergoing repeat biopsy. Whereas other studies have shown that PCA3 is a better predictor in this setting, this report raises concerns about relying on PCA3 results to predict missed cancer.

Auprich and associates[8] also looked at the PCA3 gene to assess prostate cancer aggressiveness on biopsy; 1606 men undergoing biopsy were evaluated, including 834 men undergoing repeat biopsies. Results indicated that 39.2% of the biopsies revealed prostate cancer (45.9% initial, 33% repeat). Age, serum PSA level, abnormal digital rectal examination (DRE) results, and PCA3 correlated with Gleason score $>$ 6 on initial biopsy. On multivariate analysis, only PSA and DRE results were predictive. For repeat biopsies, only PSA was predictive on multivariate analysis.

The effort to identify more specific markers for prostate cancer than PSA continues. Catalona and colleagues[9] reported on the Prostate Health Index (PHI), which is an arithmetic manipulation of the level of pro-PSA, free PSA, and total PSA. The researchers evaluated 658 men undergoing prostate biopsy. The AUC for predicting cancer for PHI was 0.703, significantly higher than PSA or percentage of free PSA (0.516 and 0.648, respectively). The economic implications of adding a third analyte (pro-PSA) to afford a 5.5% improvement in test accuracy needs to be considered.

The power of the Gleason grading system is seemingly unassailable. It remains the method to beat when considering novel markers for prognostic purposes—an enduring tribute to Dr. Donald Gleason. One problem in assessing molecular markers is preservation of the tissue characteristics that allow assurance that the marker under investigation has precise histologic control. Troyer and colleagues[10] developed a novel fixation and specimen preparation system that affords accurate histologic control of small molecule metabolite biomarkers quantitated with mass spectrometry. This may allow true advances in the development of new markers of malignant potential.

Haese and colleagues[11] examined the TMPRSS2-ERG gene fusion and its relationship to pathology at radical prostatectomy. They used a urine assay to quantitate the TMPRSS2-ERG fusion. Among 74 men, 38% had non–organ-confined disease and 93% had Gleason score $\geq$ 7. The gene fusion level was significantly higher in men with non–organ-confined disease and those with Gleason score 7 versus 6.

[Michael K. Brawer, MD]

Prostate Cancer

Prostate cancer screening was a major theme at the 2011 AUA meeting. There is now randomized evidence that PSA screening reduces prostate cancer mortality for men aged 50 to 69 years.[12,13] However, prior studies have suggested high rates of screening in elderly men with limited life expectancies who are unlikely to benefit.[14] A new report from Gupta and colleagues examined rates of PSA screening in men from the Behavioral Risk Factor Surveillance System survey (2001-2008).[15] They found that men in their 70s were more likely to undergo screening than men aged 40 to 60 years, and that approximately 60% of men aged ≥ 80 years had a PSA test in the past year. These results suggest continued overutilization of screening in elderly men, as well as potential underutilization of baseline PSA testing at a younger age.

Indeed, prior studies have shown that PSA levels at a young age are associated with the risk of prostate cancer and aggressive disease.[16,17] Vickers and colleagues presented new data from the Malmo Preventive Project in Sweden, in which a single PSA measurement at age 44 to 50 years predicted disease-specific mortality at a median follow-up of 27 years.[1] In this study, 44% of all later prostate cancer deaths occurred in men with PSA levels in the top 10% at age 44 to 50 (> 1.5 ng/mL), indicating a high-risk population for whom careful follow-up is necessary.

Another controversy is the appropriate age to discontinue screening. One recent study suggested that men with a PSA level < 1 ng/mL at age 60 years do not require further PSA testing given the low risk of metastasis and death in this patient subset.[18] In a new analysis from the Baltimore Longitudinal Study of Aging, Loeb and colleagues[19] similarly reported a low overall risk of prostate cancer (6.5%) among men with an initial PSA < 1 ng/ mL in their 60s; however, 30.8% of these cases were life threatening. Moreover, despite starting out with a PSA < 1 ng/mL, the subsequent PSA trajectory differed substantially between men without prostate cancer compared with those later diagnosed with non–high-risk and, particularly, high-risk disease. Thus, additional PSA measurements would have identified high-risk cases. However, the optimal number and timing of additional PSA screening require further study.

The topic of prostate cancer chemoprevention was also addressed at the AUA 2011 meeting. Randomized trials previously reported a reduction in prostate cancer diagnoses in men taking 5-alpha reductase inhibitors (5-ARIs).[20,21] However, it was recently estimated that treatment of 200 men with 5-ARIs would result in three fewer Gleason 6 and one additional Gleason 8 to 10 tumors, leading the US Food and Drug Administration to rule against their use in chemoprevention.[22] In one abstract, O'Brien and colleagues compared pathologic tumor features between men who were and were not taking 5ARIs prior to radical prostatectomy.[23] In this clinical cohort, they observed that long-term 5-ARI use (> 3 years) was associated with greater odds of non–organ-confined and high-grade disease in the prostatectomy specimen.

Other researchers further evaluated the relationship between 5-ARI use and long-term survival outcomes. In an abstract from Denmark, Kjellman and colleagues examined the rates of metastasis and disease-specific mortality in 5-ARI users.[24] Specifically, they compared 199 men taking 5-ARIs to 613 men using alpha-blockers and 2806 men not taking either of these medications. Overall, 5-ARI users had a significantly increased risk of metastatic disease (odds ratio [OR] 1.14; 95% confidence interval [CI], 1.01-1.29), although the difference in prostate cancer mortality did not reach statistical significance. Interestingly, alpha-blocker use was associated with a significantly lower risk of both metastases (OR 0.89; 95% CI, 0.81-0.98) and disease-specific death (OR 0.78; 95% CI, 0.67-0.9). These results corroborate prior findings from the Finnish Prostate Cancer Screening Trial, in which 5-ARIs were associated with an increased risk and alpha-blockers with a decreased risk of high-grade prostate cancer.[25]

Statins represent another type of medication under investigation for a possible role in prostate cancer chemoprevention because of numerous epidemiologic studies suggesting a decreased risk of aggressive prostate cancer. Freedland and colleagues[26] examined the association between statin use and biopsy findings in 6729 men from the Reduction of Dutasteride in Cancer Events (REDUCE) trial, of which 17.5% reported statin use. On multivariable analysis, there was no significant relationship between statin use with low-grade ($P = .62$) or high-grade ($P = .34$) prostate cancer detection on biopsy. A randomized study has not been performed to evaluate a role for statins for prostate cancer prevention. Nevertheless, these combined findings would suggest the need for ongoing active investigation into novel chemopreventive strategies.

[Stacy Loeb, MD,
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Incontinence

OnabotulinumtoxinA (Botox®; Allergan, Irvine, CA) significantly decreases episodes of urinary incontinence and improved quality of life secondary to neurogenic detrusor overactivity in patients with multiple sclerosis or spinal cord injury, according to the results of two presentations

of the Phase III studies presented at the 2011 AUA meeting.[27,28] The data show that although there were no clinically relevant differences in efficacy or duration of effect between the 200 U and 300 U doses of onabotulinumtoxinA, the lower dose had a better safety profile. The main finding is that the endpoints were reached in continence and urodynamic parameters, and there was no significant difference in efficacy between the 200 U and 300 U doses. The efficacy data were presented by David Ginsberg, MD; results of quality-of-life issues of this phase III study were also presented.

In an international, multicenter, double-blind, randomized, placebo-controlled, parallel-group study, two doses of botulinum toxin type A, onabotulinumtoxinA were evaluated for the treatment of urinary incontinence caused by neurogenic detrusor overactivity. The impact of onabotulinumtoxinA on health-related quality of life (HRQoL) and patient satisfaction were also evaluated in patients with urinary incontinence due to neurogenic detrusor overactivity. Patients with urinary incontinence and neurogenic detrusor overactivity resulting from multiple sclerosis or spinal cord injury not adequately managed with anticholinergics and with 14 or more weekly incontinence episodes were treated with intradetrusor onabotulinumtoxinA (200 or 300 U) or placebo. Patients were followed for up to 64 weeks and could request retreatment once from week 12 onward. The primary endpoint was the change from baseline in weekly incontinence episodes at week 6. Secondary endpoints included changes from baseline in maximum cystometric capacity and maximum detrusor pressure during first involuntary detrusor contraction. Changes in HRQoL were recorded by the Incontinence Quality of Life questionnaire (I-QOL) and a modified Overactive Bladder Patient Satisfaction with Treatment Questionnaire (OAB-PSTQ).

Patients (416) were randomized to receive 30 intradetrusor injections (1 mL each) of onabotulinumtoxinA, 200 U or 300 U, or placebo, performed through a cystoscope and avoiding the trigone. Patients had the option of discontinuing anticholinergics before the study or remaining on therapy. For those continuing on anticholinergics, the same dose had to be maintained throughout the study. Individuals using clean intermittent catheterization at baseline were instructed to maintain their established frequency. Individuals not using self-catheterization had to be willing to initiate it if necessary.

The subjects had a mean age of 46 years with 30.5 weekly urinary incontinence episodes at baseline, and were randomized to receive placebo (n = 149) or onabotulinumtoxinA, 200 U (n = 135) or 300 U (n = 132). There were no significant differences between groups in baseline characteristics or urodynamic parameters.

Results showed that the median time to a request for retreatment was 92 days in the placebo group, 256 days in the 200 U group, and 254 days in the 300 U group, respectively. OnabotulinumtoxinA, 200 U, decreased the number of weekly urinary incontinence episodes by 21.0 ± 23.8 episodes/week. OnabotulinumtoxinA, 300 U, reduced weekly incontinence episodes significantly more than placebo (22.7 ± 17.1 vs 8.8 ± 16.2 episodes, respectively). Remarkably, 36% and 41% of patients in the 200 U and 300 U groups, respectively, became dry at week 6, compared with 10% of the placebo group ($P < .001$).

Results were similar irrespective of anticholinergic use. Significant reductions in urinary incontinence episodes were also observed in both the spinal cord injury and multiple sclerosis subgroups.

When compared with placebo, in both onabotulinumtoxinA groups, maximum cystometric capacity significantly increased ($P < .001$) and maximum detrusor pressure during the first involuntary detrusor contraction significantly decreased ($P < .001$). No clinically meaningful or statistical differences in efficacy were noted between the two onabotulinumtoxinA groups.

Overall, 34%, 49%, and 50% of patients in the placebo, 200 U, and 300 U dose groups, respectively, developed urinary tract infections, and 3%, 20%, and 17% experienced urinary retention. In patients not using clean intermittent catheterization at baseline, 7%, 28%, and 40%, respectively, had initiated self-catheterization at 6 weeks.

Results also showed mean improvements from baseline in the 22-item I-QOL; overall scores were significantly greater ($P < .001$) in both the onabotulinumtoxinA groups (200 U [+27], 300 U [+33]) compared with the placebo group (+11) at week 6. Responses to the 16-item modified OAB-PSTQ indicated significantly greater mean improvements from baseline in both the onabotulinumtoxinA 200 U (−39) and 300 U (−44) groups versus the placebo group (−11) at week 6.

Significantly more onabotulinumtoxinA-treated patients were satisfied with treatment, achieved their primary treatment goals, and met or exceeded their treatment expectations compared with placebo-treated patients. Finally, no clinically relevant differences between the two onabotulinumtoxinA doses were observed.

Patients treated with 200 U or 300 U onabotulinumtoxinA showed greater changes in original OAB-PSTQ scores compared with the placebo group. Likewise, patients treated with 200 U or 300 U onabotulinumtoxinA were more likely to answer that they were "somewhat satisfied" or "very satisfied"

with treatment compared with the placebo group. About three quarters of patients in all three treatment groups reported no side effects, and this was similar among all groups.

[Jayabalan Nirmal, PhD, Michael B. Chancellor, MD]

Chronic Prostatitis/Chronic Pelvic Pain Syndrome and Bladder Pain Syndrome/ Interstitial Cystitis

The AUA annual meeting again this year provided a forum for researchers in chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) and interstitial cystitis (bladder pain syndrome) syndromes to further our understanding and improve our therapy for these enigmatic conditions. There were many excellent basic scientific studies that provide a ground-breaking foundation for future understandings and therapies; however, this review will focus on advancements in therapy that are practical now or will be in the near future.

Electromagnetic stimulation (EMS) has been suggested in the past as a treatment for men with CP/CPPS, particularly for those who did not respond to pharmacotherapy. Thirty-seven of 46 men with CP/CPPS who underwent electromagnetic stimulation were available for analysis. With very few adverse events (AEs), three-quarters of the patients who completed therapy reported a positive answer to benefit. Sixty percent had perceptible improvement based on the decrease of the CP symptom index score. This study did suggest that EMS may be a reasonable treatment option for CP/CPPS patients who do not respond to drug therapy.[29]

Pelvic muscle tenderness is frequent in patients with CP/CPPS and previous reports from the AUA suggest that pelvic myofascial physical therapy is helpful. A unique and innovative internal therapeutic trigger point wand, which allows patients self-treatment, was investigated in 113 of 169 patients who completed 6 months of use. This curved wand serves as an extended finger to locate and release painful myofascial trigger points and incorporates an integrated algometer sensor to monitor point pressure and prevent excessive or dangerous force. There were no serious side effects and rare transient episodes of mucosal bleeding. The majority of patients who completed 6 months of therapy indicated that they were very satisfied or moderately satisfied with the use of the wand. This self-treatment utilizing a therapeutic wand for myofascial trigger point release appears to be a safe and viable CPPS management option.[30]

Nerve growth factor (NGF) levels correlate with pain severity in CP/CPPS. Tanezumab, a humanized monoclonal antibody, selectively inhibits NGF. Safety and efficacy (pain and symptoms) of tanezumab were assessed in a double-blind, randomized, placebo-controlled proof of concept study. Overall, 62 patients with CP/CPPS were randomized to receive active treatment or placebo. At week 6, tanezumab marginally improved average daily pain and urgency and episodes of frequency versus placebo, but this was not statistically proven. Eighty percent of tanezumab versus 65.6% of placebo patients experienced an AE with paresthesia being the most common AE in the tanezumab group (26.7% vs 6.3% in the placebo group). This exploratory study suggests that tanezumab might provide some symptom improvement compared with placebo for patients with CP/CPPS; however, it does not appear to provide significant benefit for an unselected CP/CPPS population. These findings support additional efforts to define which patient phenotypes may prove amenable to NGF-directed therapy.[31]

Over the years, a number of trials evaluating alpha-blockers have been presented at the AUA, with variable results. Silodosin, a uroselective alpha-blocker, was evaluated in a double-blind, placebo-controlled, phase II study in men with moderate to severe CP/CPPS. Of 151 participants, 76.2% completed the study. The National Institutes of Health-Chronic Prostatitis Symptom Index (NIH-CPSI) total score decreased significantly with silodosin, 4 mg, compared with placebo. Interestingly, there was a significant benefit in the physical quality-of-life score in the silodosin, 4 mg, group compared with placebo. In addition, 56% of patients receiving silodosin, 4 mg, versus 29% receiving placebo reported a marked or moderate improvement during global response assessment; 26.9% of patients receiving silodosin, 4 mg, experienced retrograde ejaculation (vs placebo at 1.9%). Treatment with silodosin, 8 mg, provided no additional clinical benefit. The results suggest that silodosin, 4 mg, may provide an effective treatment option for patients with CP/CPPS; however, like all monotherapies, only a modest improvement can be shown in the unselected CP/CPPS population and it is expected that better results would be seen when used as part of a directed multimodal therapeutic program.[32]

Previous reports, including studies presented at the AUA, suggest that a decrease in coffee intake provides significant benefit in patients with painful bladder syndrome/interstitial cystitis (PBS/IC). It is generally accepted that coffee (and its equivalents) exacerbates symptoms of PBS/IC. A study was presented this year at the AUA to define the relationship between caffeine and IC symptoms by assessing changes in irritative voiding symptoms and pelvic pain in patients randomized to receive either a pill containing 100 mg of caffeine or placebo. In this trial, in which 30 patients with PBS/IC were enrolled, no significant difference was found in pain or global

assessment at each time interval assessed between the two groups after administration of caffeine or placebo. Although caffeine has been associated with symptom exacerbation and PBS/IC, this particular randomized, placebo-controlled, double-blind study did not demonstrate a difference in irritative voiding symptoms or difference in voiding volume with caffeine and it is suggested that there may be other components of coffee that might be the culprit.[33]

Immunotherapy, including cyclosporine and mycophenolate, has been evaluated in the past for bladder pain syndrome/interstitial cystitis (BPS/IC) with variable results. Cyclosporine A appears to be the most promising immunotherapy for this use and this agent was offered off-label to 19 treatment-refractory BPS/IC patients and the results reviewed retrospectively. Fourteen of the 19 patients reported a 70% average global improvement in their symptoms. Cyclosporine A was effective in the majority of refractory BPS/IC patients in this real-life, clinical practice evaluation. The authors suggest that potential clinical markers to predict a cyclosporine response would include the presence of Hunner's lesions or associated collagen vascular disease. They do warn that, although cyclosporine A was generally well tolerated, careful monitoring is required.[34]

Researchers from Italy have investigated the efficacy of intravesical instillation of a naturally occurring peptide, nociceptin/orphanin FQ (N/OFQ) for the treatment of BPS/IC. Twenty-three subjects with BPS/IC received N/OFQ twice a week for 4 weeks by intravesical instillation. The authors noted a statistically significant decrease in the O'Leary-Sant IC problem index but not the O'Leary-Sant IC symptom index. There was a decrease in Visual Analogue Scale (VAS) and about half of the patients were satisfied with the results of treatment. These preliminary results suggest that N/OFQ may provide benefit to patients with BPS/IC and certainly further randomized, placebo-controlled trials would be mandatory to confirm this initial impression.[35]

Intratrigonal injection of botulinum toxin A has been reported in patients with BPS/IC who have been refractory to first-line therapy. Investigators evaluated the therapeutic effect of repeated intratrigonal injection of onabotulinumA in 14 women with BPS/IC refractory to first-line treatment. The patients received four consecutive intratrigonal injections under general anesthesia. The investigators reported that all patients reported subjective improvement following each injection and that each treatment provided symptomatic relief for a period of between 9 and 12 months. No cases of voiding dysfunction or urinary retention were reported. This study suggested that intratrigonal injection of botulinum toxin A is safe, effective, and has a maintained effect after repeated injection in patients with treatment refractory BPS/IC.[36]

Two studies that were more basic science in nature suggested further therapeutic avenues that should be explored in BPS/IC. A study with mice showed that treatment with selective cannabinoid receptor 2 (CB2) agonists reduced the severity of acrolein-induced cystitis and inhibited bladder inflammation–induced increased peripheral sensitization to mechanical stimuli. The data would indicate that CB2 might play an inhibitory role in bladder inflammation and subsequent changes in pain perception. CB2 agonists have been developed and clinical trials are being initiated in 2011 for this particular indication.[37]

Another interesting and somewhat innovative basic science study investigated the beneficial effects of honey on histamine release from LAD2 cells. Honey has long been used for the treatment of wounds and has more recently demonstrated to have beneficial effects on wound healing. Mechanisms include antibacterial properties, cytokine interaction, and antioxidant effects as well as on mass cell activity. The investigators concluded that a constituent of most honeys inhibits spontaneous and stimulated mass cell degranulation in a cell line model. Certainly this interesting observation warrants further investigation as a possible intravesical agent in the treatment of BPS/IC.[38]

Pentosan polysulphate (PPS) is one of the few oral medications approved for the treatment of interstitial cystitis. The authors of this study investigated 107 cats with a history of recurrent feline interstitial cystitis, a naturally occurring animal model of bladder pain in humans. A prospective, multicentered, double-blind, placebo-controlled randomized trial between multiple doses of PPS and placebo showed highly statistically and clinically significant improvement of lower urinary tract symptoms (LUTS) in all cats treated with PPS, regardless of dose. This study confirms the benefits of one of our standard therapies in a similar disease in another species.[39]

[J. Curtis Nickel, MD, FRCSC]

Infertility

Of all the patients who undergo sperm extraction procedures for in vitro fertilization (IVF), the nonobstructive azoospermic (NOA) patients are the ones that create the most emotional distress not only for themselves, but also for the urologist. There is never any certainty that one will be able to find sperm within the testes and in those situations where sperm cannot be found when both testes have been thoroughly microdissected, the testes themselves may be at risk for

androgenic failure secondary to the surgical procedure itself. Therefore, it would be a godsend if one would be able to "see" within the testes with the naked eye (albeit under an operating microscope) whether sperm are present. This would direct the urologist to only those places within the testicular parenchyma with the highest likelihood of finding sperm, which in theory spares the rest of the testes from damage during the microdissection and would also make a 2- to 3-hour procedure take less than 1 hour to perform.

To this end, Ramasamy and colleagues presented their experimental animal data using multiphoton microscopy (MPM) to "see" the areas of the testicular tubules where sperm may be present.[40] In this in vitro setting they were able to guess accurately by the florescence produced by their microscope in which testes sperm could be found.

Although this study was an in vitro animal study, it heralds the beginning of the evaluation of tools that may aid the urologist in delineating which areas within the testes have the highest likelihood of having sperm. Such an option within the urologist's armamentarium will go a long way in building confidence both with the urologist and the infertile couple as they determine their best option for treating NOA.

[Jacob Rajfer, MD]

Pediatric Urology

The pediatric urology State of the Art Lectures by Dr. Michael Ritchey and Dr. William Brock were very informative. Dr. Ritchey delivered a comprehensive presentation entitled, "The Urologic Malignancies in Children: Long-Term Implications for Adults." He noted that there are now 250,000 survivors of urologic cancer. The Childhood Cancer Survivor Study predicts that 73% will develop one or more chronic health problems and over one-third will have a severe or life-threatening condition involving the heart, lungs, or nervous system linked to their successful childhood therapies. There are numerous late effects of treatment including fertility problems, bladder dysfunction (rhabdomyosarcoma [RMS]), and renal failure (Wilms tumor [WT]). In addition, second malignant neoplasms occur in 3% to 6% at 20 years following diagnosis.[41] Irradiation and alkylating agents are primary risk factors for these secondary tumors. The risk increases over time, with 12% of WT survivors developing second malignancies at 50 years. The secondary malignancies include bone cancer, breast cancer, thyroid cancer, central nervous system (CNS) tumors often occurring 10 or more years later, as well as leukemia, following treatment with alkylating agents or topoisomerase II inhibitors.[42] Renal cell carcinoma has occurred in survivors of neuroblastoma and WT.[41,43]

Post-treatment fertility problems can occur due to surgical injury to genital structures, neurologic impairment, cranial or gonadal irradiation, and chemotherapy. Although the ovary is relatively radioresistant to chemotherapy, ovarian failure can develop after abdominal irradiation. It is dose related and can result in delayed puberty and premature menopause.[44] Premature menopause can also occur after chemotherapy. In males, hypogonadism and temporary azoospermia can result following gonadal radiation.[45] Although Leydig cells are more radioresistant than germ cells, high-dose radiotherapy can lead to inadequate testosterone production and delayed sexual maturity. Alkylating agents can also result in testicular dysfunction.[46] Semen preservation should be considered in the pubertal male, and testicular cryopreservation has recently been reported.[47]

In women who undergo abdominal/pelvic irradiation, pregnancy outcomes may be affected, with increased rates of miscarriage and prematurity and lower birth weight infants reported.[48] Chemotherapy alone does not appear to adversely affect pregnancy.

Bladder dysfunction can result from pelvic or CNS surgery, pelvic irradiation, or alkylating agent chemotherapy such as cyclophosphamide. It is usually seen in patients with bladder/prostate RMS. Yeung and colleagues studied the effects of irradiation in 11 patients with pelvic RMS who had bladder preservation followed for a mean of 6.6 years.[49] Seven of these children received radiation therapy and all had reduced bladder capacity (11%-48%) and enuresis, whereas four children who did not receive radiation had normal bladder function. A later study by Raney and coworkers reported continence outcomes in 164 patients over age 6 years of age with bladder/prostate RMS followed for a median of 8 years.[50] Of the 62 patients who did not undergo cystectomy, 31% were incontinent. Of the 44 patients who underwent partial cystectomy, 27% were incontinent. Only 11 patients underwent urodynamics and 8 of the studies were abnormal.

End-stage renal disease (ESRD) is one of the more serious complications in patients with WT who have undergone bilateral nephrectomy, have decreased renal mass and subsequent hyperfiltration injury, radiation nephritis, chemotherapy-induced nephropathy, vascular injury (surgical or radiation), or nephropathy associated with WT-related syndromes.[51] ESRD occurs in >15% of bilateral WT at 16 years, with bilateral nephrectomy for progressive disease being the most common cause. This is in contrast to unilateral WT, in which renal failure develops in only 0.6% at 16 years,

with Denys-Drash syndrome (DDS) being the most common cause. DDS is associated with ambiguous genitalia, nephrotic syndrome, and WT. The most common renal lesion in DDS is diffuse mesangial sclerosis.

The incidence of renal failure in DDS and WAGR ("WAGR" is an acronym for the most common features of this disorder: ***W***ilms' tumor, ***A***niridia, ***G***enitourinary anomalies, ***R*** [developmental delay/s]) at 20 years was 62.4% and 38.3%, respectively.[52] This is significantly increased when compared with the incidence of renal failure in patients with genitourinary (GU) anomalies or unilateral WT (10.9% and 1.0%, respectively).

WT-1 is important in the development of kidney and genitalia.[53] Patients with DDS have WT-1 defects that are missense mutations that block the normal activity of the protein and lead to a progressive nephropathy. WT-1 mutations are also seen in 25% of patients with WT and GU anomalies. WAGR syndrome has a germline deletion of WT-1. WAGR and GU anomalies have a reduced WT-1 dosage during embryogenesis with a less prominent effect on renal development in contrast to DDS.

Dr. Ritchey concluded his presentation by discussing a recent study by Lange and colleagues, which examined the risk factors for ESRD in patients with WT without known WT-1–related syndromes (which excludes DDS, WAGR, and GU anomalies).[54] They hypothesized that patients with characteristics suggestive of a WT-1 etiology (age $<$ 24 months, predominant stromal histology, intralobar nephrogenic rests) would have a higher risk of ESRD from chronic renal failure. They also predicted a high risk of ESRD due to progressive bilateral WT in patients with metachronous bilateral disease. ESRD occurred in 100 of 7950 nonsyndromic patients enrolled in the National Wilms Tumor Study conducted from 1969 to 2002. These investigators found that the incidence of ESRD due to chronic renal failure 20 years after WT diagnosis was 0.7%. In those cases with ESRD due to progressive bilateral WT, the incidence was 4.0% at 3 years after diagnosis in patients with synchronous bilateral WT versus 19.3% in those with metachronous bilateral WT. They concluded that metachronous bilateral WT is associated with high rates of ESRD due to surgery for progressive WT. This may be due to the remaining kidney developing resistant disease from prior exposure to chemotherapy. Characteristics associated with a WT-1 etiology markedly increased the risk of ESRD due to chronic renal failure despite the low risk in non–WT-1 syndromic cases overall.

Although prospective, randomized studies are needed, renal-sparing surgery is recommended in patients with increased risk of bilateral disease, including syndromic patients, infants with nephrogenic rests, or multicentric disease. In addition, patients at increased risk of renal failure including those with aniridia, dialysis disequilibrium syndrome, GU anomalies, or solitary kidney should be considered for renal-sparing interventions.

Because adult survivors of pediatric GU cancers transitioning to adult care risk not having regular surveillance for complications associated with their cancer therapy, education of patients and their families will ensure optimal long-term care and treatment of these individuals.

Dr. William Brock's State-of-the-Art Lecture was entitled, "Fetal Intervention Report Card: Congenital Adrenal Hyperplasia, Posterior Urethral Valves, and Meningomyelocele." Dr. Brock graded our progress for these three conditions.

Congenital adrenal hyperplasia (CAH) occurs in 1 in 15,000 births and has an autosomal recessive inheritance.[55] Because genital development occurs between 7 and 12 weeks of gestation, fetal exposure to excess endogenous androgen leads to virilization in a 46,XX fetus. Pharmacotherapeutic intervention theoretically affords the opportunity to improve the phenotype of the fetus if there is a sibling who has been affected by CAH. Dexamethasone has been used to suppress the fetal pituitary adrenal axis thereby preventing conversion of glucocorticoid metabolites to androgens and to reduce or prevent virilization in the female. Dexamethasone is administered orally to the mother and is initiated immediately after pregnancy confirmation. If the fetus is found to be female, it is continued throughout the remainder of gestation. Most pregnancies are confirmed by 5 weeks of gestation. In families with a history of CAH, dexamethasone is initiated during this period of time. The fetal karyotype is usually confirmed by about 10 weeks using chorionic villus sampling or at 15 to 17 weeks through amniocentesis. The administration of dexamethasone leads to an increase in fetal cortisol levels to 10% of maternal levels by midgestation, which may exceed physiologic fetal levels by 60-fold.[56] Dexamethasone has the advantage of decreasing genital virilization and the subsequent need for complex genital reconstruction, in addition to reducing androgen imprinting in the developing female fetal brain. In contrast, because there is a delay between treatment initiation and karyotype confirmation of the fetal sex and CAH diagnosis, there is unnecessary exposure to glucocorticoids in seven of eight fetuses. The effect of this in the long term is unknown. There are few studies that examine the genital outcomes following dexamethasone administration. The largest series, published a decade ago by New and colleagues, screened 532 pregnancies of which 105 were affected with

classic CAH.[57] Dexamethasone was administered in 84 with CAH and 197 without CAH. Speiser and colleagues published multidisciplinary experts' concerns of the potential of unnecessary dexamethasone fetal exposure as well as the unknown long-term effects of high-dose glucocorticoids administration.[56] The long-term effects of fetal glucocorticoid expression in animal studies include orofacial clefts, adrenal and placental steroid derangement, CNS effects, low birth weight, and cardiovascular effects. In humans, cleft palate and psychological effects including cognitive impairment have been reported. At this time, CAH clinical practice guidelines state that dexamethasone administration in this setting is experimental, and institutional review board approval is needed with investigation of its use in a multiinstitutional setting. Dr. Brock concluded that the grade for fetal intervention for CAH was "incomplete" at this time.

The next urologic problem reviewed was posterior urethral valves (PUV). Dr. Brock noted that after 16 weeks of gestation, amnionic fluid was primarily composed of fetal urine.[58,59] Lower urinary tract obstruction, therefore, had consequences for survival, fetal lung development, and fetal renal development. In the 1980s, there was tremendous enthusiasm for fetal bladder drainage, including fetal vesicostomy, fetal cystoscopy with valve ablation, and vesicoamniotic shunt.[58,59] In 1986, the International Fetal Surgery Registry reported 41% overall survival in 73 cases and 76% survival in cases with PUV.[60] The remainder of the data was of very poor quality. In the 1990s, we became more selective about who should be shunted and stratified patients into prognostic categories based on serial fetal urine electrolytes.[61,62] Recently, Morris and associates reviewed 20 intervention series published between 1983 and 2005 for lower urinary tract obstruction.[63] Most of the patients underwent vesicoamniotic shunting. Intervention was performed in 369 fetuses for urethral atresia, prune belly syndrome, and PUV. Morris and colleagues reported that intervention was only beneficial in cases with a poor prognosis. In their review, only 89 (25%) fetuses underwent intervention for a diagnosis of postnatally confirmed PUV. This review poses the question whether the outcomes of these 89 fetuses and 20 studies over 22 years provide sufficient information to make informed decisions regarding fetal intervention for PUV. They also asked which valve population derives the greatest benefit from intervention and which prognostic factors were most useful in selecting patients for intervention.

Further, they evaluated the renal outcomes in five of the series.[63] Of the 30 surviving fetuses with postnatally confirmed PUV, 17 (56%) had renal insufficiency and 10 (30%) had undergone renal transplantation or transplantation evaluation. Currently, the Percutaneous Shunting in Lower Urinary Tract Obstruction (PLUTO) trial randomizes patients to conservative management versus shunt placement and will provide 5-year follow-up.[64] How have we performed in the area of treatment of PUV? Over the past 20 years, we have not performed very well, according to Dr. Brock. These fetal interventions may have improved survival by improving pulmonary development, but there remains significant high risk for long-term renal morbidity. The ideal fetus for intervention with lower urinary tract obstruction remains unknown at this time.

The third condition evaluated was prenatal treatment of myelomeningocele. In order to minimize the neurologic defects in myelomeningocele, fetal myelomeningocele closure has been advocated since 1999, when Bruner and colleagues published a retrospective case-control study of 29 prenatal closures versus 30 postnatal controls, showing that prenatal closure led to a significant decrease in hindbrain herniation (57%) and a decrease for ventriculoperitoneal shunting (VPS) (32%).[65] In addition, a delayed time to shunt placement was observed. Another study of 50 fetuses by Johnson and colleagues also found a significant decrease in VPS when compared with controls (43% vs 85%).[66] The fetal meningomyelocele closure study began in 2003 (http://www.spinabifidamoms.com). Prenatal closure was performed prior to 26 weeks at three centers and an outcome assessment of 12-month outcomes included fetal or neonatal death or the need for VPS. Accrual was terminated at the end of 2010 when efficacy was achieved. In February 2011, Adzick and coworkers reported that fetal closure resulted in a 30% reduction in death or need for VPS and a 42% reduction in actual VPS placement.[67] Over time, they also observed improved motor function and development scores. At this time, none of the centers have shown improvement in bladder function when compared with historic controls. Prenatal treatment for meningomyelocele has been one the greatest accomplishments in fetal diagnosis and treatment. We have also learned from this trial that federal funding is needed to design and implement randomized, controlled trials that will generate meaningful data to advance our treatment of complex problems.

[Ellen Shapiro, MD, FACS, FAAP]

LUTS and Benign Prostatic Hyperplasia (BPH)

LUTS and BPH once more received considerable attention at the national meeting of the AUA. The presentations were divided into sessions on basic research, epidemiology and natural history/evaluation and markers,

and a podium session on medical and hormonal therapy, surgical therapy, and new technology. In addition, information relevant to male voiding dysfunction, LUTS, and BPH were also presented in the five sessions of general and epidemiological trends, socioeconomics, and the sessions on evidence-based medicine and outcomes, practice patterns, and cost-effectiveness/quality of life issues. Parenthetically, it is of interest to note that over time, practice patterns and cost-effectiveness has increased from an occasional presentation to three sessions at the 2011 meeting, reflecting the increasing awareness and the importance of cost-effectiveness in urology practice.

Basic Research

Twenty posters were presented in a session on basic research. Several presentations again focused on the relationship between inflammation and LUTS and BPH. Yoo and colleagues from Korea showed a strong association between interleukin (IL) 10, 10RA, and 10RB polymorphism and BPH in a Korean population, again emphasizing the strong relationship that inflammatory gene expression has with the severity of LUTS and BPH.[68]

A group from France and the Netherlands presented (messenger) mRNA data and showed that certain genes in the tissue of patients with histological inflammation were significantly upregulated at the mRNA level; these genes were CCR7, CD40LG, CGLA4, and ICOS. Because it is obviously not practical to biopsy each patient to identify the presence or absence of inflammation, the authors attempted to identify whether any of these genes could also be measured in the urine. As it turns out, inducible T-cell costimulator (ICOS) was easily measured by enzyme-linked immunoabsorbent assay (ELISA) in urine and at the protein level and it was associated with a higher postvoid residual urine and a lower maximum urinary flow rate. Clearly, efforts such as these linking easily measured genes or gene products that are associated with inflammation of the prostate could be helpful in predicting which patients may have a worse or accelerated natural history.[69]

There is a paucity of appropriate models for LUTS and BPH and two groups presented their research regarding a mouse and rat model of BPH. Ricke and coworkers utilized both testosterone and estradiol and created a mouse model for BPH with findings consistent with bladder outlet obstruction. The hope is that such models will make it easier to dissect the molecular mechanisms involved in the pathophysiology of BPH and to test the therapeutic targets used to prevent or treat obstructive signs and symptoms of BPH.[70]

Oudot and colleagues presented a new experimental rat model combining LUTS/BPH and erectile dysfunction (ED) by giving testosterone supplementation to spontaneously hypertensive rats (SPHR). This is the first experimental model presenting both prostate enlargement and ED and could be of great interest considering the common coexistence of both ED and LUTS in the aging male population.[71]

Epidemiology and Natural History/Evaluation and Markers

Wu and Aaronson from San Francisco examined the national incidence and outcomes of postoperative urinary retention in a surgical care improvement project (SCIP).[72] SCIP is a national quality partnership of organizations charged with improving the safety and quality of surgical care; SCIP measures are followed in most hospitals across the country. Postoperative urinary retention following nonurological procedures is a common morbidity following surgery in up to 41% of cases. The authors examined a database of over 415,000 patients and identified risk factors for postoperative urinary retention. They found that 2.1% of the patients developed postoperative retention and those who did had a higher risk of urinary tract infections (UTIs), a longer length of stay (LOS), and greater costs associated with posthospitalization care. Risk factors were increased age and knee and hip surgery, as well as colon surgery and several comorbidities including chronic kidney disease, depression, paralysis, and complicated diabetes. Although there are currently no immediate practical consequences from this knowledge, surgeons performing such higher risk procedures in elderly and diabetic patients may wish to consider preventive steps such as using alpha-adrenergic receptor blockers, which have been shown to help with postoperative retention. However, there are no data yet to demonstrate that preventative administration of such drugs would reduce or eliminate the frequency of such occurrences.

Two presentations examined body weight, physical activity, urinary symptoms, and BPH. Parsons and associates reported from the Urologic Diseases in America project about the relationship between body weight, physical activity, and urinary symptoms in older men and found that excess body weight is associated with a decrease in physical activity and an increased risk of incident LUTS.[73]

Eifler and colleagues from Johns Hopkins examined the relationship between BMI in younger men with prostate enlargement later in life in the Baltimore Longitudinal Study of Aging (BLSA). Their findings suggest that younger men with elevated BMI are more likely to develop an enlarged prostate later in life, with the greatest

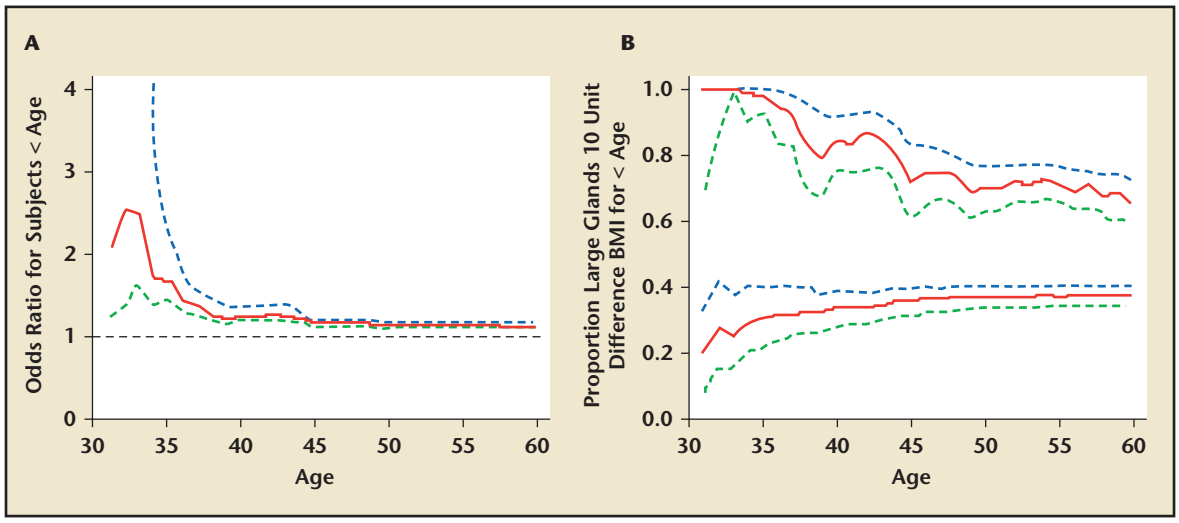


Figure 1. (A) *Odds ratio (OR) of developing an enlarged prostate for men with an elevated body mass index (BMI) who are less than a given age. Men at age<35 years had a particularly high OR, but as older men were included in the population, the OR decreased. Hashed lines represent 95% confidence intervals.* (B) *Proportion of men projected to have an enlarged prostate. Men with a BMI 10 units above the median are more likely to develop an enlarged prostate, particularly if they are young. Reproduced with permission from Eifler et al.*[74]

association between BMI and later prostate volume observed in men younger than age 35 years with elevated BMI (Figure 1).[74]

St. Sauver and coworkers reported from the Olmsted County Study of Urinary Symptoms in Men that at least one aspect of the weight/LUTS and BPH relationship does not hold true: modest weight loss is not associated with improvements in LUTS.[75]

Much has been written in recent years about the relationship between lipid-lowering drugs from the statin class and a variety of issues relating to prostate diseases, from elevated serum PSA levels to mortality from prostate cancer to LUTS and BPH. It had been hypothesized that statins may help LUTS through anti-inflammatory or other pathways and the New England Research Institutes (NERI) group examined whether the use of statins improved LUTS. In the Boston Area Community Health (BACH) Study Group, they observed that current statin use appears to predict clinically relevant LUTS score improvement, but not progression. In addition, they found that gender-specific differences may suggest that the protective effect of current statin use may be through the prostate or at least male-specific pathways (Figure 2).[76]

A separate presentation from the BACH study by Araujo and colleagues examined the role of sleep in the development of LUTS. Incident LUTS were related to short sleep duration among men and restless sleep among men and women and incident urge incontinence and nocturia were both related to restless sleep among women. The findings remained persistent after adjustment for BMI and C-reactive protein (CRP). The authors concluded that sleep is clearly a modifiable risk factor that precedes the development of urological symptoms over a 5-year period, perhaps operating through inflammatory and other pathways as measured by CRP.[77] It should be noted that in the Section of Epidemiology and Natural History, three other abstracts dealt with the issue of nocturia, which is finally receiving the attention that it rightfully deserves.[78-80]

An interesting poster was presented by Stroup and coworkers, who examined hospital discharge trends in the United States from 1998 to 2007 for BPH patients. BPH accounted for 8% of admissions, with an increasing trend despite a decrease in primary admission for BPH; this is likely a result of decreases in surgery and a shift to outpatient procedures (Figure 3). However, the frequency of BPH associated with acute renal failure, urinary retention, bladder stones, and UTIs among hospital inpatients has not declined, and an area of widespread use of medical therapy and the prevalence of acute renal failure increased in the observation period by more than 400%.[81] The authors cite this as a potential explanation for medication-driven decreases in the frequency of AEs which were offset by an increase in BPH incidence and a greater number of BPH-associated events. They also speculated that medication delayed onset, but not the probability of progression.

These observations are also echoed in a paper published by Izard and Nickel in 2010 following a presentation

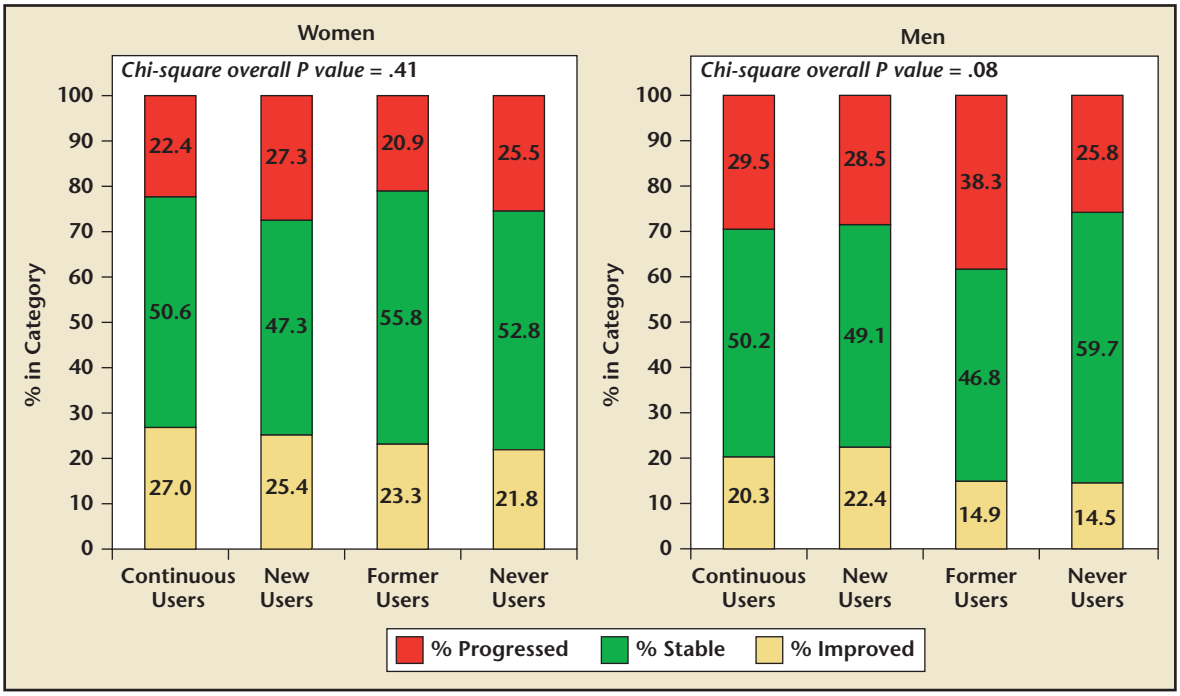


Figure 2. *American Urological Association symptom index score change comparing T1 to T2, by gender and statin use category (unadjusted for age). Reproduced with permission from Hall et al.*[76]

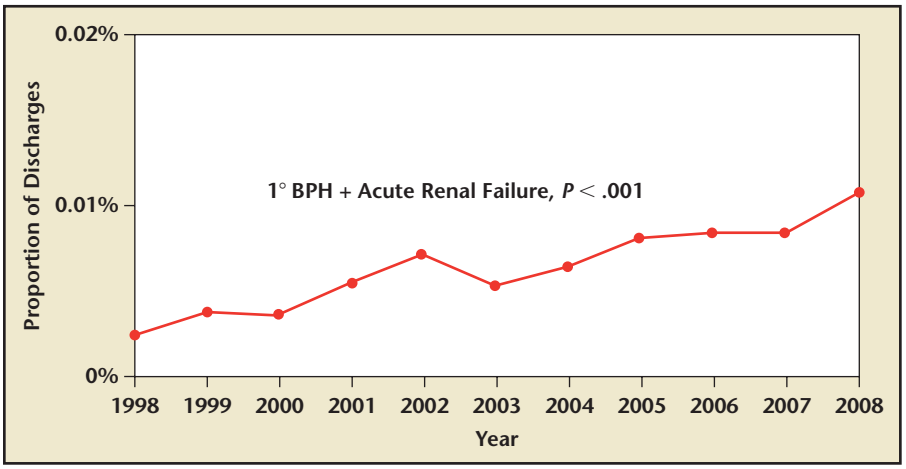


Figure 3. *The frequency of benign prostatic hyperplasia associated with acute renal failure, urinary retention, bladder stones, and urinary tract infections among hospital inpatients has not declined and an area of widespread use of medical therapy, and the prevalence of acute renal failure increased in the observation period by more than 400%. Reproduced with permission from Stroup et al.*[81]

at that year's AUA.[82] In a single center, they observed that during the time period from 1988 to 2008, there was a significant rise in patients presenting with acute or chronic urinary retention at transurethral resection of the prostate (TURP) and a significant increase in the number of patients who were discharged with a catheter for failure to void. The number increased from 3.2 in 1988 to 12.5 in 1998 and 28.6 in 2008. These data may support the observation and speculation by Stroup that medical therapy occasionally may unintentionally lead to delay in diagnosis and surgical treatment that then may lead to a window for cure missed (Table 1).

Another reference related to this topic studies the use patterns of and adherence to medications for BPH.[83] These authors describe a relatively poor adherence for LUTS and BPH medications (Figure 4). After approximately 1 year, 40% of patients had discontinued their medications; the discontinuation rates were highest for alpha-blockers compared with finasteride or multiple medications. Again, a physician may prescribe medication for a patient with LUTS and there might be several unintended consequences: the patient may not take the medication for very long and, when it eventually comes to a surgical procedure, the patient may not have the same probability of ultimate improvement, may have a higher likelihood for presentation in urinary retention, and a greater likelihood for an initial failure to void spontaneously.

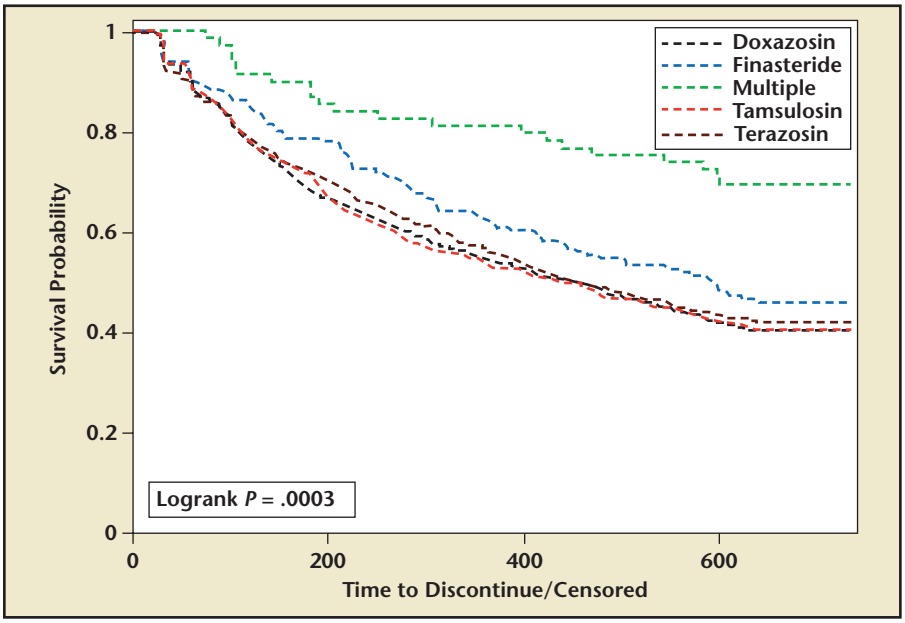
The NERI facility in Boston introduced urologists to the concept of

Table 1
Impact of Medical Therapy on Transurethral Resection of the Prostate: Two Decades of Change

	1988 (N =157)	1998 (N = 64)	2008 (N = 84)
Preoperatative BPH-related events % (*n*)			
AUR	22.9 (36)	54.7 (35)[a]	42.9 (36)[a]
CUR	14.6 (23)	20.3 (13)	39.3 (33)[a,b]
Hydronephrosis	1.3 (2)	12.5 (8)[a]	7.1 (6)[3]
UTI	14.0 (22)	9.4 (6)	13.1 (11)
Operative Parameters			
Age, years	70.8 ± 1.43	70.7 ± 2 .00	72.9 ± 1.77
ASA class	2.42 ± 0.11	2.20 ± 0.16[a,c]	2.54 ± 0.15
Weight of tissue resected, g	16.5 ± 1.9	12.5 ± 2.5[a]	12.9 ± 2.7
Operative time, min	59.0 ± 3.9	59.2 ± 6.5	44.4 ± 5.2[a,b]
Postoperative in-hospital course			
Catheter removed (days)*	2.6 ± 0.48	1.9 ± 0.35	1.3 ± 0.26[a,b]
Postoperative days in hospital	4.1 ± 0.35	2.7 ± 0.46[a]	2.1 ± 0.92[a]
Postoperative complications, % (*n*)			
Catheterized on discharge†	3.2 (5)	12.5 (8)[a,c]	28.6 (24)[a,b]
Postoperative Complications‡	14.6 (23)	9.4 (6)	31.0 (26)[a,b]

ASA, American Society of Anesthesiologists; AUR, acute urinary retention; BPH, benign prostatic hyperplasia; CUR, chronic urinary retention; UTI, urinary tract infection.
*Postoperative day on which the patient's urinary catheter was removed.
†Patients who failed a trial of voiding and who were discharged with a urinary catheter to be removed at a later date.
‡Patients requiring an extended hospital stay, repeated surgery, readmission to the hospital, or an emergency department visit.
[a]Statistically significant compared with 1988 ($P < .05$).
[b]Statistically significant compared with 1998 ($P < .05$).
[c]Statistically significant compared with 2008 ($P < .05$).
Data presented as the mean ± 95% CI, unless otherwise specified.
Reproduced with permission from Izard and Nickel.[82]

Figure 4. *Poor adherence with medications for lower urinary tract symptoms and benign prostatic hyperplasia. Reproduced with permission from Nichol et al.*[83]



cluster analyses. At this year's meeting, Rosen and colleagues presented a poster reporting cluster patterns identified in the BACH study in male and female participants. The specific question was how much change occurs in the pattern of symptoms over time.[84] The investigators found that the likelihood of progression from one cluster to the next highest cluster is significantly associated with age. Cluster remission was associated with age and International Prostate Symptom Score (IPSS) category in men. The cluster analysis in the BACH study published by the NERI group in several publications and presented at this year's meeting drew considerable attention to the importance of comorbid conditions not only with regard to the baseline severity of symptoms, but also for the likelihood of progression. In fact, the number of comorbid conditions, particularly in the male population, seems to be of greatest importance in predicting whether a man is likely to progress from one cluster to the next (Figures 5 and 6).

Medical Therapy

Several abstracts were presented that examined medical therapy alone or in combination for male voiding dysfunction and BPH. Lee and colleagues[85] from Korea described a prospective, randomized, multicenter, double-blind, placebo-controlled study combining anticholinergics with alpha-adrenergic receptor blockers in men with bladder outlet obstruction (BOO) secondary to BPH as well as overactive bladder. This was a 12-week trial of 176 Korean men who received doxazosin, 4 mg, plus placebo or doxazosin, 4 mg, plus tolterodine, 4 mg, daily for 12 weeks. Compared with the placebo group, the combination group showed significant reductions in the storage subscore of the IPSS and improvement in the quality-of-life item as well as

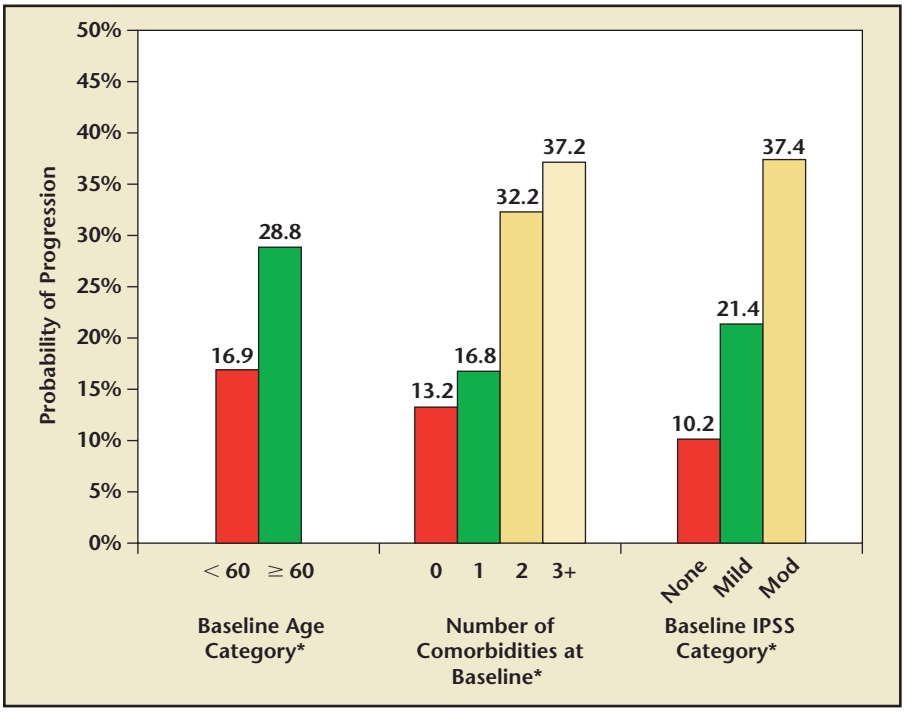


Figure 5. *The number of comorbid conditions, particularly in the male population, seems to be of greatest importance in predicting whether a man is likely to progress from one cluster to the next. Reproduced with permission from Rosen et al.*[84]

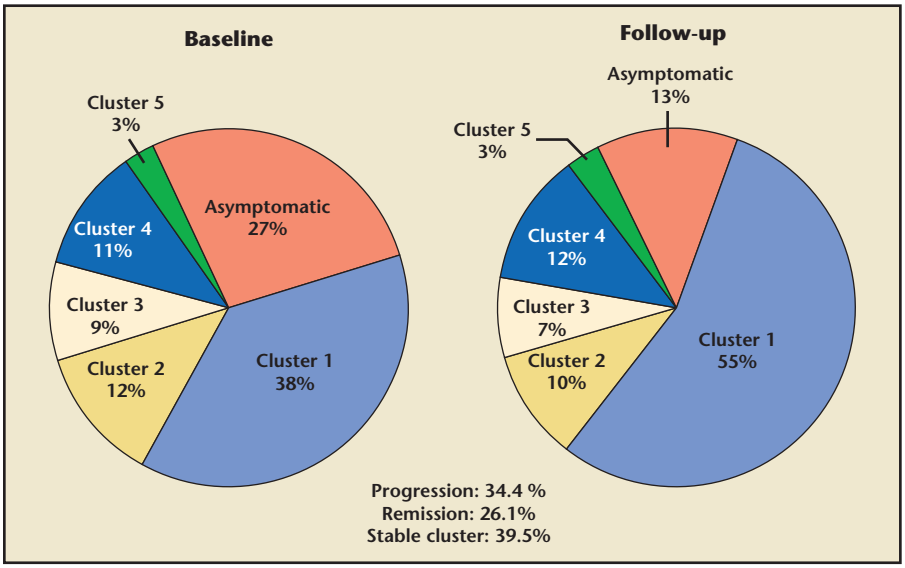


Figure 6. *The likelihood of progression from one cluster to the next highest cluster is significantly associated with age. Reproduced with permission from Rosen et al.*[84]

urgency episodes and micturition frequency at weeks 4 and 12. The risk of urinary retention was not increased, but it has been observed by others who performed similar studies with different or the same medications. It does appear that the combination of an alpha-blocker and anticholinergics is used particularly in men with mostly storage or irritative symptoms with the caveat that none of these trials are particularly long in duration. The trials also excluded men with particularly large prostates, highly obstructive symptom scores, and increased residual urine. Thus, it is the safety of the treatment in the long term that is in question, not the efficacy in the short term.

Kruep and colleagues examined the impact of the length of 5-ARI therapy in clinical outcomes and costs in a population of managed care patients. They used the market scan commercial Medicare supplemental database and considered men who were given a 5-ARI prescription between 2003 and 2009. Over 54,000 patients were identified, with a mean age of 68.5 years. The authors demonstrated by multivariate analysis that each additional 30 days of 5-ARI therapy was associated with a 14% reduced risk of acute urinary retention (AUR), an 11% reduced risk of surgery, and a 13% reduced risk of clinical progression. The BPH-related medical costs decreased by 15% for every 30-day increase in therapy after controlling for baseline characteristics. The findings, provocative as they were, suggested that over a long duration of time, 5-ARI treatment in appropriately chosen patients may be quite cost effective. The study was funded by GlaxoSmithKline, maker of Avodart® and Jalyn™.[86]

Along a similar line, Westerman and coworkers examined the cost-effectiveness of 5-ARI–induced chemoprevention on both undisclosed GU symptoms and prostate cancer. They developed a marker model with health states for prostate cancer, undisclosed BPH, and clinically managed BPH beginning at age 50 years. Without chemoprevention and using a 5-ARI, 20.4% of men in the model would be diagnosed with prostate cancer over their lifetime, with a 3%

prostate-cancer–specific mortality. On a 5-ARI, the incidence of mortality decreased to 16.5% and 2.5%, respectively. At age 70 years, the model predicted 28.5% prevalence of undisclosed BPH, which without chemoprevention would be reduced by 50% using 5-alpha reductase inhibition. The model was sensitive to drug price and the incremental cost-effectiveness ranged from $28,170 for quality adjusted life year to over $88,000 for quality adjusted life year. Clearly, marker modeling is not real life; however, when carefully performed it can project the impact of medical interventions on a larger population. The authors who presented these provocative findings declared no source of funding.[87]

Chang and colleagues presented a retrospective study of 620 patients with BPH who were prescribed an alpha-blocker and/or 5-ARI as first treatment between January 1989 and July 2000. Following these patients for more than 10 years, the researchers calculated the incidence of AUR and BPH-related surgery in the alpha-blocker–only group and the combination group. Three hundred and sixty-eight men received only an alpha-blocker and 252 received combination therapy. AUR was experienced in 13.6% in the former and 2.8% in the latter group ($P \leq .001$). Surgery for BPH was performed in 8.4 versus 3.2 ($P = .008$). The incidence of AUR in BPH-related surgery was thus reduced by 85.2% and 77.2%, respectively, when the prostate volume was larger than 35 g, and by 84.3% and 77.6%, respectively, when the PSA level was greater than 2.0.[88] These data add to the growing body of evidence that combination medical therapy with an alpha-blocker and 5-ARI, particularly in men with large glands and elevated serum PSA levels, is both clinically effective as well as cost-effective by reducing the incidence of outcomes and complications such as retention and surgery.

A side-by-side comparison of the populations from the Combination of Avodart and Tamsulosin (CombAT) and the REDUCE trials was presented by Roehrborn and colleagues. The patients were stratified for both studies by prostate size, which ranged from less than 30 cc to over 80 cc; the REDUCE trial did not enroll patients with a prostate size of over 80 g and the CombAT trial did not enroll patients with a prostate size under 30 g. As Figure 7 demonstrates, there is an incremental increase in AUR and BPH-related surgery noted in nondutasteride treatment groups, which represents the tamsulosin-treated patients in CombAT and the placebo-treated

Figure 7. (A) *Acute urinary retention (AUR)/benign prostatic hyperplasia (BPH)–surgery rates increase with prostate volume in nondutasteride groups.* (B) *AUR/BPH-related surgery rates were similarly low in dutasteride groups. DUT, dutasteride; TAM, tamsulosin. Reproduced with permission from Roehrborn et al.*[89]

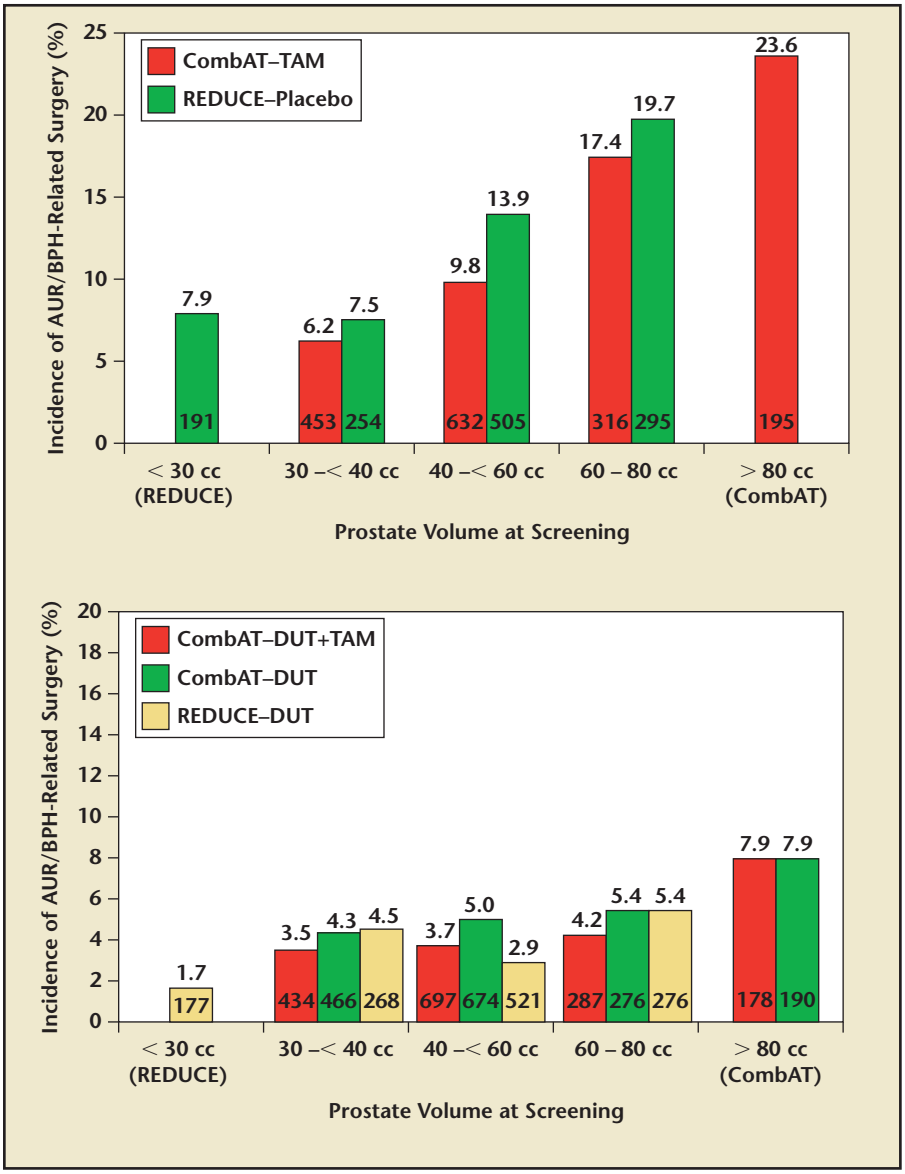


Table 2
Effects of Silodosin in Men With Moderate or Severe Chronic Prostatitis/Chronic Pelvic Pain Syndrome

	Silodosin, 4 mg (n = 52)	Silodosin, 8 mg (n = 45)	Placebo (n = 51)
NIH-CPSI Total Score			
Baseline, mean ± SD	26.0 ± 6.3	26.8 ± 5.9	27.9 ± 6.2
Change from baseline, mean ± SD	−12.1 ± 9.3	−10.2 ± 8.8	−8.5 ± 7.2
P value vs placebo	.022	.591	
Marked or moderate improvement in GRA			
At week 12,* n (%)	29 (55.8)	15 (33.3)	15 (29.4)
P value vs placebo	.007	.679	

GRA, global response assessment; NIH-CPSI, National Institutes of Health Chronic Prostatitis Index; SD, standard deviation.
Reproduced with permission from Nickel et al.[32]

patients in REDUCE. Furthermore, there was virtually no difference between the tamsulosin-treated patients in CombAT and the placebo-treated patients in REDUCE within each volume category. Both groups of patients receiving dutasteride either alone (CombAT dutasteride or REDUCE dutasteride arm) or in combination (CombAT dutasteride plus tamsulosin arm) showed a significant reduction in AUR and BPH-related events. It is noteworthy that in the volume range from 30 cc to 80 cc, the incidence rate was almost identical across volume stratification, suggesting that the relative risk reduction is greatest in patients who are at greatest risk—those with larger prostates and analogously higher PSA values.[89]

I would like to mention one abstract from the prostatitis section, a presentation by Nickel and colleagues on the effects of the alpha-blocker silodosin in men with moderate or severe CP or CPPS. This double-blind, placebo-controlled, phase II study showed a significant improvement in the NIH CPSI total score from baseline in patients treated with silodosin, 4 mg, versus placebo (−12.1 vs −8.5). The patients in the silodosin, 4 mg, group also experienced marked or moderate improvement in the global subjective assessment in a significantly higher proportion compared with the placebo-treated patients (Table 2). It remains to be seen whether Watson Pharmaceuticals will conduct a properly designed and empowered phase III study utilizing silodosin either in a 4-mg or an 8-mg dose for the treatment of CPPS.[32]

BPH Surgical Therapy and New Technology

Thirty-two abstracts were presented in two sessions on surgical therapy and new technology. Doctors Lee and Lerner from Massachusetts examined the surgical management of BPH by way of a 90-item online survey mailed by the AUA, the Veterans Administration, and the Society for Government Service Urologists to 600 urologists. The goal was to compare the utilization of 12 surgical techniques. A total of 600 urologists replied with 570 currently performing BPH surgery. The percentages of urologists utilizing the various procedures are: open prostatectomy (OP) at 78% of respondents; monopolar TURP, 73%; photoselective vaporization (PVP), 58%; button TURP, 24%; bipolar TURP, 20%; holmium laser enucleation of the prostate (HoLEP), 18%; thulium laser ablation of the prostate, 4%; and laparoscopic (LP) and robotic (RP) simple prostatectomy at 1% and 3%, respectively. When stratified by urologist age, there are no differences in utilization of monopolar TURP or OP, and laser therapies are employed across all age ranges. However, RP is only used by urologists younger than age 50 years. The authors did not observe differences in type of procedures performed in the full-time academic versus nonacademic setting except for RP and button TURP, which was more often used in academic settings. Of interest, the frequency of any type of BPH surgery is relatively low, with over half of the respondents doing less than 50 procedures per year: 1 to 24 per year, 23.4%; 25 to 49 per year, 32.1%; 50 to 74 per year, 22.5%; and more than 75 per year, 22.%.[90]

Three abstracts described endovascular superselective embolization of prostatic arteries as the new method to treat LUTS and BPH less invasively. Kurbatov presented data on 65 patients with moderate to severe symptoms and reported an improvement in the AUA Symptom Score from 21.8 to 7.3 points. Similarly, peak urinary flow rates were significantly improved. Figure 8 demonstrates angiography before and after embolization of the right and the left prostatic artery.[91]

da Motta and coworkers reported on prostatic arterial embolization as the primary treatment for BPH and Pinheiro reported short- and medium-term outcomes for the same procedure.[92,93]

This reviewer cannot help but feel that superselective embolization of the prostatic artery may not be as minimally invasive as portrayed by the authors and it remains to be seen

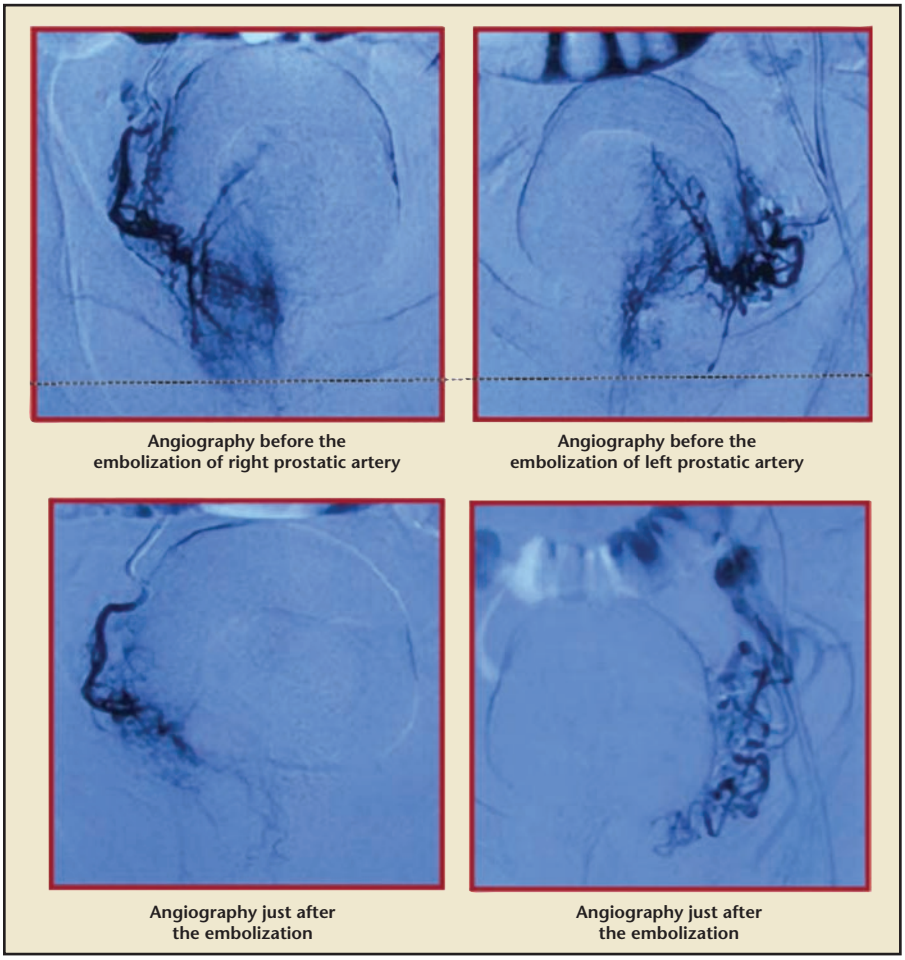


Figure 8. *Angiography before and after embolization of the right and left prostatic artery. Reproduced with permission from Dedov et al.*[91]

in the long term whether it fulfills the goals of a truly effective and safe minimally invasive treatment. Concerns are not only the possibility of inadvertently embolizing the wrong artery, but also the question as to whether an embolization of the prostate leads to a fibrotic or stiff prostate as a result of ischemia-induced necrosis that may not allow for improved urine flow. Long-term data from other centers will be needed to verify whether this technique will stand the test of time.

When scanning the literature and the abstracts in these two sessions, it does appear that physicians are attempting to use various energy sources for enucleation of the prostate. The term *enucleation* was introduced by Gilling and coworkers, and is associated with the HoLEP procedure. At this year's meeting, Chughtai and associates compared the technique for transurethral laser prostatectomy with a standard PVP with the transurethral laser enucleation of the prostate, a procedure they called TLEP.[94] Yang and Chang used the diode laser to enucleate the prostate as an alternative to a standard TURP.[95]

Again, it remains to be seen whether other energy sources are as effective as the HoLEP. Certainly, Professor Elhilali in Montreal is a master of the HoLEP procedure and his group presented several abstracts. One of them focused on the HoLEP procedure versus photoselective vaporization using the GreenLight laser at a 120W setting for prostatic glands larger than 60 mL. They found that, in terms of IPSS and quality of life, the outcomes at 1 year are relatively similar, although the HoLEP procedure induces a greater improvement in peak urinary flow rate (Figure 9).[96]

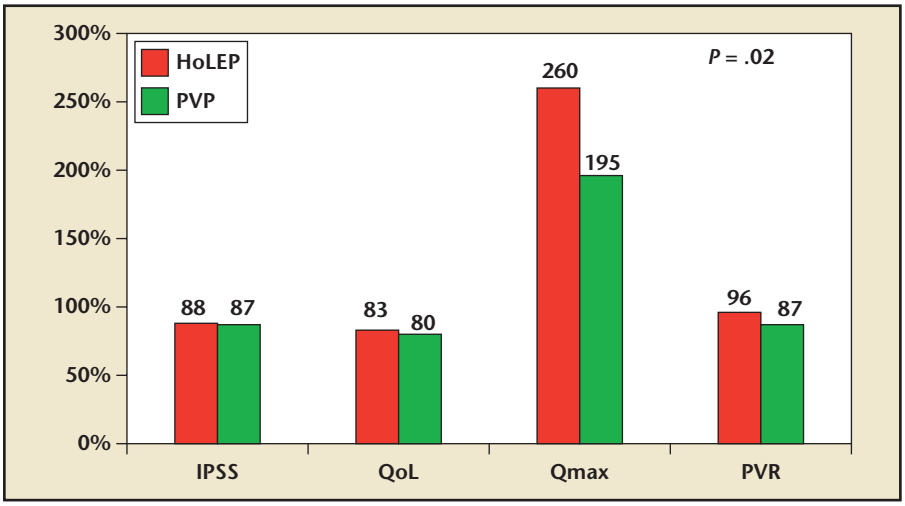


Figure 9. *Percentage of improvement in clinical outcomes at 1 year follow-up, according to intent-to-treat analysis. HoLEP, holmium laser for the enucleation of the prostate; IPSS, International Prostate Symptom Score; PVP, photoselective vaporization of the prostate; PVR, postvoid residual urine volume; QoL, quality of life; Qmax, peak urinary flow rate. Reproduced with permission from Elmansy et al.*[96]

The same group also examined the long-term durability of clinical outcomes and complications rate over 10 years in a large patient cohort.[97] In a retrospective analysis of 952 patients treated between 1998 and 2010 in a single center, the authors reported a mean follow-up of 62 months, a Q_{max} improvement to 24, 24, and 27 mL/s at 1 month, 1 year, and 10 years, respectively. Stress incontinence was found in the first 3 months in 4.9%, with only 0.5% experiencing stress incontinence at the latest follow-up visit. Bladder neck contractures and urethral strictures were rare in 0.8 and 1.6 of patients only. Reoperation rates were exceedingly uncommon at 0.7%, whereas in standard TURP series reoperation rates are estimated to be 1% per year.

In the same session, the group from Montreal also reported specifically on stress urinary incontinence following HoLEP and examined possible ways to predict and/or prevent it.[98] In their analysis, they found that the presence of diabetes mellitus, large prostate volume, and greater reduction in PSA (ie, more complete enucleation of tissue), remains statistically significant for the development of stress urinary incontinence. The authors recommend an early start with Kegel exercises in the immediate postoperative period or even preoperatively (there are no data to support this claim) and offer modifications to the HoLEP procedure to decrease the rate of stress urinary incontinence (Figure 10).

Regarding GreenLight or KTP PVP, Zorn and colleagues presented mid-term outcomes of 250 cases performed in a single center with the GreenLight 120W HPS laser. Stratified by prostate volume (less than 60, 60-100, and over 100 cc), improvement was reported in symptom score at 1 year by 69%, 63%, and 50%, and in peak flow rate by 194%, 175%, and 162%, respectively. The authors deem these improvements as significant and durable and acknowledge that larger prostates require significantly more time and energy.[99]

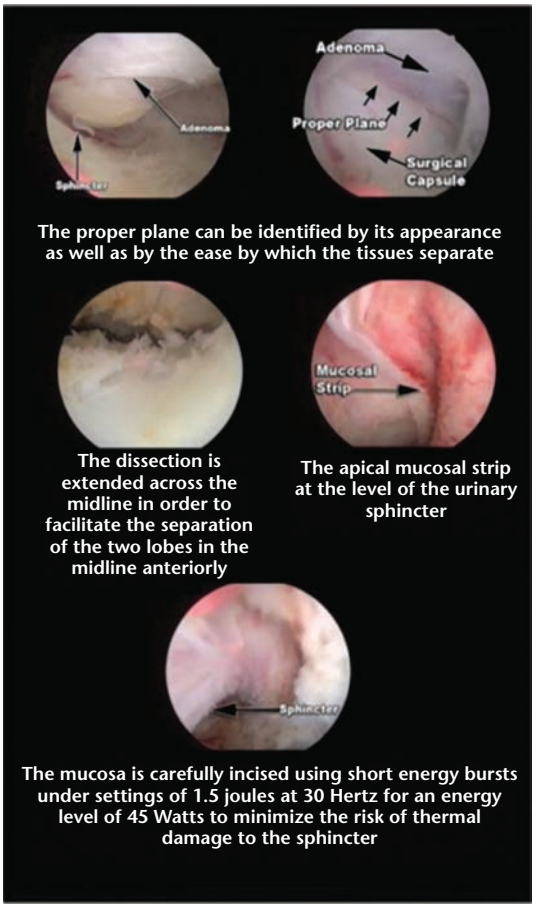


Figure 10. *Modifications to the holmium laser enucleation procedure to decrease the rate of stress urinary incontinence. Reproduced with permission of Elmansy et al.*[98]

The brand new 180W XPS laser received considerable attention on the trade show floor, but was also represented in an abstract presented by Woo and colleagues, who reported on an international, multicenter experience with this particular technology.[100] Since June 2010, the availability date for the laser, 60 consecutive patients underwent 180W XPS PVP with the liquid-cooled MoXy laser fiber. The participating sites included Basel, Switzerland; Boston, Massachusetts; Madrid, Spain; Sydney, Australia; San Francisco, California; and London, UK. The population was a typical BPH population with a mean age of 69.8 years, Q_{max} of 8.7 mL/s, prostate volume of 67.8, serum PSA level of 5.8 ng/mL, and an IPSS score of 22.1. After an observation period limited by necessity to 3 months, Q_{max} improved to 17.9, and IPSS declined to 6.5. No reoperations occurred, but the follow-up period is short. The authors found in early experience that the high-powered 180 W laser provided better handling and greater fiber durability with more rapid and visible tissue ablation with improved coagulation properties. Long-term data obviously are needed to verify these findings.

Finally, a comment regarding an innovative procedure, the UroLift® System Treatment, developed by NeoTract (Pleasanton, CA). Woo and

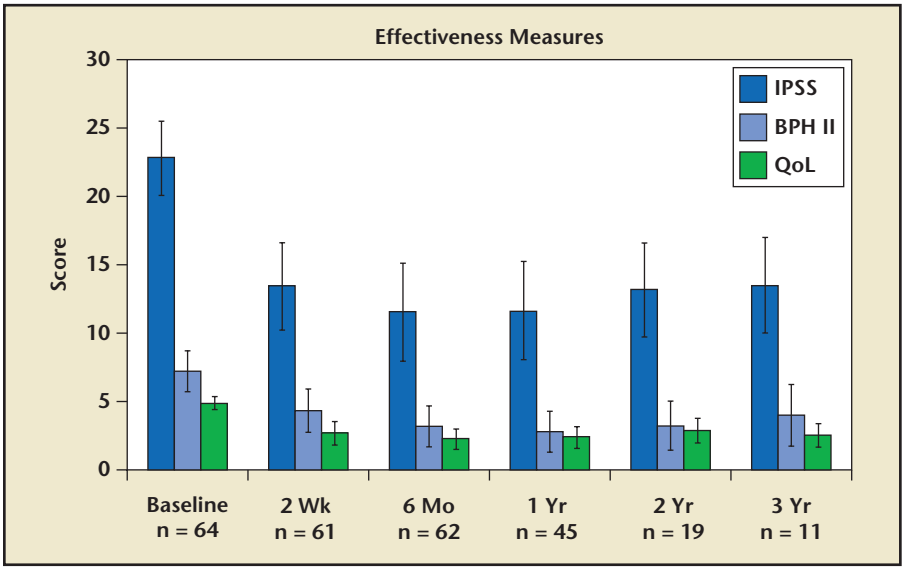


Figure 11. *International Prostate Symptom Score (IPSS), benign prostatic hyperplasia (BPH) II, and quality of life (QoL) measures demonstrate sustained reduction through 3 years of follow-up. ($P < .05$ for all displayed values). Reproduced with permission from Woo et al.*[100]

colleagues presented a multicenter experience focusing on the first 64 patients who were treated primarily in Australia. Follow-up was available for 45 patients at 1 year and 19 patients at 2 years, with 11 patients having reached 3 years of follow-up. Symptom score improvements seemed to be sufficient and durable (Figure 11). The company has initiated an international, multicenter, randomized, sham-controlled (randomization 3:1 active vs sham) trial that has just started in the United States. The data from this trial will determine whether the technology will be submitted for approval to the FDA.[101]

Overall, the 2011 AUA Annual Meeting in Washington, DC, provided an opportunity to learn more about the basic science, epidemiology, and natural history of LUTS and BPH as well as a host of medical and device treatments with their respective outcomes. In addition, LUTS and BPH are also conditions often examined in the sessions on cost-effectiveness and practice patterns.

[Claus G. Roehrborn, MD, FACS]

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